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1 Child SJ et al. Int J Cancer 1990 Mar 15;45(3):457-61

2 Press MF et al. Oncogene 1990 Jul; 5(7):953-62

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Thanks

Christopher Yaen
Patent Examinier
Art Unit 1642, Rm 4D14
Mail Box 8E12
703-305-3586

1973830

1: Oncogene 1990 Jul;5(7):953-62

Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues.

Press MF, Cordon-Cardo C, Slamon DJ.

Department of Pathology, University of Southern California, Los Angeles 90033.

The HER-2/neu proto-oncogene is homologous with, but distinct from, the epidermal growth factor receptor. Current evidence indicates that this gene is frequently amplified and/or overexpressed in some human breast and ovarian cancers and that these alterations may be clinically important; however, little is known about the expression pattern of the gene in normal tissues. Using immunohistochemistry and northern blot analyses to identify the HER-2/neu protein and transcript respectively, we have evaluated a variety of normal adult and fetal tissues for HER-2/neu expression. HER-2/neu protein was identified on cell membranes of epithelial cells in the gastro-intestinal, respiratory, reproductive, and urinary tract as well as in the skin, breast and placenta. Northern hybridization confirmed the presence of the 4.5 kb transcript encoding the protein in these tissues. The amount of HER-2/neu message and protein was generally higher in fetal tissues than in the corresponding normal adult tissues. HER-2/neu expression levels in these normal tissues were similar to the levels found in non-amplified, non-overexpressing breast cancers and breast cancer cell lines. Southern hybridization of extracted DNA showed that none of the normal tissues expressing HER-2/neu had amplification of the gene. These results confirm that HER-2/neu is normally a membrane constituent of a variety of epithelial cell types.

PMID: 1973830 [PubMed - indexed for MEDLINE]

1: Cancer Res 1995 Oct 15;55(20):4586-93 Related Articles, NEW Books, LinkOut

Phase I trial of 2B1, a bispecific monoclonal antibody targeting c-erbB-2 and Fc gamma RIII.

Weiner LM, Clark JI, Davey M, Li WS, Garcia de Palazzo I, Ring DB, Alpaugh RK.

Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, USA.

2B1 is a bispecific murine monoclonal antibody (BsMAb) with specificity for the c-erbB-2 and Fc gamma RIII extracellular domains. This BsMAb promotes the targeted lysis of malignant cells overexpressing the c-erbB-2 gene product of the HER2/neu proto-oncogene by human natural killer cells and mononuclear phagocytes expressing the Fc gamma RIII A isoform. In a Phase I clinical trial of 2B1, 15 patients with c-erbB-2-overexpressing tumors were treated with 1 h i.v. infusions of 2B1 on days 1, 4, 5, 6, 7, and 8 of a single course of treatment. Three patients were treated with daily doses of 1.0 mg/m2, while six patients each were treated with 2.5 mg/m2 and 5.0 mg/m2, respectively. The principal non-dose-limiting transient toxicities were fevers, rigors, nausea, vomiting, and leukopenia. Thrombocytopenia was dose limiting at the 5.0 mg/m2 dose level in two patients who had received extensive prior myelosuppressive chemotherapy. Murine antibody was detectable in serum following 2B1 administration, and its bispecific binding properties were retained. The pharmacokinetics of this murine antibody were variable and best described by nonlinear kinetics with an average t 1/2 of 20 h. Murine antibody bound extensively to all neutrophils and to a proportion of monocytes and lymphocytes. The initial 2B1 treatment induced more than 100-fold increases in circulating levels of tumor necrosis factor-alpha, interleukin 6, and interleukin 8 and lesser rises in granulocyte-monocyte colony-stimulating factor and IFN-gamma. Brisk human anti-mouse antibody responses were induced in 14 of 15 patients. Several minor clinical responses were observed, with reductions in the thickness of chest wall disease in one patient with disseminated breast cancer. Resolution of pleural effusions and ascites, respectively, were noted in two patients with metastatic colon cancer, and one of two liver metastases resolved in a patient with metastatic colon cancer. Treatment with 2B1 BsMAb has potent immunological consequences. The maximum tolerated dose and Phase II daily dose for patients with extensive prior

1: Br J Cancer 1993 Dec;68(6):1140-5

Monoclonal antibodies directed to the erbB-2 receptor inhibit in vivo tumour cell growth.

Harwerth IM, Wels W, Schlegel J, Muller M, Hynes NE.

Friedrich Miescher Institute, Basel, Switzerland.

Four monoclonal antibodies (MAbs) specific for the extracellular domain of the human erbB-2/HER2 protein (FRP5, FSP16, FWP51 and FSP77) have been isolated (Harwerth et al., J. Biol. Chem., 267, 15160-15167, 1992). In this paper we describe the effects of erbB-2 specific MAb administration on the tumorigenic growth of human erbB-2 transformed NIH3T3 cells implanted into athymic nude mice. Two antibodies, FWP51 and FSP77, inhibited the onset of tumour growth, while the administration of FRP5 and FSP16 did not affect tumour growth. In addition, administration of MAbs FWP51 and FSP77 led to a retardation in the growth of established tumours. Treatment was not curative in that tumours regrew within two weeks of the final treatment. The administration of a combination of MAbs FWP51 and FSP77 which react with two distinct regions on the erbB-2 molecule was more effective than treatment with either MAb alone. The two growth-inhibitory antibodies were also effective in the treatment of tumours established from SKOV3 cells, a human ovarian tumour cell line with high levels of the erbB-2 protein. The effect of the MAbs on the anchorage-independent growth of erbB-2 transformed cells and on erbB-2 receptor turnover was also measured.

PMID: 7903153 [PubMed - indexed for MEDLINE]

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1: J Clin Oncol 1996 Mar;14(3):737-44

Comment in:
- J Clin Oncol. 1996 Mar;14(3):697-9

Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer.

Baselga J, Tripathy D, Mendelsohn J, Baughman S, Benz CC, Dantis L, Sklarin NT, Seidman AD, Hudis CA, Moore J, Rosen PP, Twaddell T, Henderson IC, Norton L.

Department of Medicine, Services of Breast and Gynecological Cancer Medicine and Clinical Immunology, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

PURPOSE: Breast cancer frequently overexpresses the product of the HER2 proto-oncogene, a 185-kd growth factor receptor (p185HER2). The recombinant humanized monoclonal antibody (rhuMAb) HER2 has high affinity for p185HER2 and inhibits the growth of breast cancer cells that overexpress HER2. We evaluated the efficacy and toxicity of weekly intravenous administration of rhuMAb HER2 in patients with HER2-overexpressing metastatic breast cancer. PATIENTS AND METHODS: We treated 46 patients with metastatic breast carcinomas that overexpressed HER2. Patients received a loading dose of 250 mg of intravenous rhuMAb HER2, then 10 weekly doses of 100 mg each. Patients with no disease progression at the completion of this treatment period were offered a maintenance phase of 100 mg/wk. RESULTS: Study patients had extensive metastatic disease, and most had received extensive prior anticancer therapy. Adequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients. Objective responses were seen in five of 43 assessable patients, and included one complete remission and four partial remissions (overall response rate, 11.6%; 95% confidence interval, 4.36 to 25.9). Responses were observed in liver, mediastinum, lymph nodes, and chest wall lesions. Minor responses, seen in two patients, and stable disease, which occurred in 14 patients, lasted for a median of 5.1 months. CONCLUSION: rhuMAb HER2 is well tolerated and clinically active in patients with HER2-overexpressing metastatic breast cancers that had

received extensive prior therapy. This is evidence that targeting growth factor receptors can cause regression of human cancer and justifies further evaluation of this agent.

Publication Types:

- Clinical Trial
- Clinical Trial, Phase II

PMID: 8622019 [PubMed - indexed for MEDLINE]

1: J Clin Oncol 1995 Sep;13(9):2281-92

Phase Ia/Ib trial of bispecific antibody MDX-210 in patients with advanced breast or ovarian cancer that overexpresses the proto-oncogene HER-2/neu.

Valone FH, Kaufman PA, Guyre PM, Lewis LD, Memoli V, Deo Y, Graziano R, Fisher JL, Meyer L, Mrozek-Orlowski M, et al.

Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA.

PURPOSE: MDX-210 is a bispecific antibody that binds simultaneously to type I Fc receptors for immunoglobulin G (IgG) (Fc gamma RI) and to the HER-2/neu oncogene protein product. MDX-210 effectively directs Fc gamma RI-positive effector cells such as monocytes and macrophages to phagocytose or kill tumor cells that overexpress HER-2/neu. The goals of this phase Ia/Ib trial were to determine the maximum-tolerated dose (MTD) and/or the optimal biologic dose (OBD) of MDX-210. PATIENTS AND METHODS: Patients with advanced breast or ovarian cancer that overexpressed HER-2/neu were eligible for treatment. Cohorts of three patients received a single intravenous (IV) infusion of MDX-210 at increasing dose levels from 0.35 to 10.0 mg/m2. RESULTS: Treatment was well tolerated, with most patients experiencing transient grade 1 to 2 fevers, malaise, and hypotension only. Two patients experienced transient grade 3 hypotension at 10.0 mg/m2. Transient monocytopenia and lymphopenia developed at 1 to 2 hours, but no other hematologic changes were observed. Doses of MDX-210 > or = 3.5 mg/m2 saturated > or = 80% of monocyte Fc gamma RI and produced peak plasma concentrations > or = 1 microgram/mL, which is greater than the concentration for optimal monocyte/macrophage activation in vitro. Elevated plasma levels of the monocyte products tumor necrosis factor alpha (TNF alpha), interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), and neopterin were observed with maximal levels at doses > or = 7.0 mg/m2. Localization of MDX-210 in tumor tissue was demonstrated in two patients. One partial and one mixed tumor response were observed among 10 assessable patients. CONCLUSION: MDX-210 is immunologically active at well-tolerated doses. The MTD and OBD is 7 to 10 mg/m2.

Publication Types:

1: J Clin Immunol 1991 May;11(3):117-27 Related Articles, NEW Books, LinkOut

Monoclonal antibody therapy of human cancer: taking the HER2 protooncogene to the clinic.

Shepard HM, Lewis GD, Sarup JC, Fendly BM, Maneval D, Mordenti J, Figari I, Kotts CE, Palladino MA Jr, Ullrich A, et al.

Department of Developmental Biology, Genentech, Inc., South San Francisco, California 94080.

The HER2 protooncogene encodes a 185-kDa transmembrane protein (p185HER2) with extensive homology to the epidermal growth factor (EGF) receptor. Clinical and experimental evidence supports a role for overexpression of the HER2 protooncogene in the progression of human breast, ovarian, and non-small cell lung carcinoma. These data also support the hypothesis that p185HER2 present on the surface of overexpressing tumor cells may be a good target for receptor-targeted therapeutics. The anti-p185HER2 murine monoclonal antibody (muMAb) 4D5 is one of over 100 monoclonals that was derived following immunization of mice with cells overexpressing p185HER2. The monoclonal antibody is directed at the extracellular (ligand binding) domain of this receptor tyrosine kinase and presumably has its effect as a result of modulating receptor function. In vitro assays have shown that muMAb 4D5 can specifically inhibit the growth of tumor cells only when they overexpress the HER2 protooncogene. MuMAb 4D5 has also been shown to enhance the TNF-alpha sensitivity of breast tumor cells that overexpress this protooncogene. Relevant to its clinical application, muMAb 4D5 may enhance the sensitivity of p185HER2-overexpressing tumor cells to cisplatin, a chemotherapeutic drug often used in the treatment of ovarian cancer. In vivo assays with a nude mouse model have shown that the monoclonal antibody can localize at the tumor site and can inhibit the growth of human tumor xenografts which overexpress p185HER2. Modulation of p185HER2 activity by muMAb 4D5 can therefore reverse many of the properties associated with tumor progression mediated by this putative growth factor receptor. Together with the demonstrated activity of muMAb 4D5 in nude mouse models, these results support the clinical application of muMAb 4D5 for therapy of human cancers characterized by the overexpression of p185HER2.

Publication Types:

1: J Immunol Methods 1995 Apr 12;181(1):37-43 Related Articles, Books, LinkOut

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Stability of monoclonal IgM antibodies freeze-dried in the presence of trehalose.

Draber P, Draberova E, Novakova M.

Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague.

We describe the use of the disaccharide trehalose for stabilization of mouse monoclonal IgM antibodies during freeze-drying and prolonged storage at elevated temperatures. Spent culture media, ascitic fluids and isolated immunoglobulins were freeze-dried in the presence of trehalose, stored at different temperatures, and tested after rehydration for their binding to their corresponding antigens. Antibodies, directed against various types of antigens, effectively recovered their binding efficiency as tested in enzyme-linked immunoassays, flow cytometry and immunofluorescence. Application of trehalose for freeze-drying of labile monoclonal IgM antibodies permits convenient long-term storage of large quantities of antibodies, facilitates their transport at ambient temperature and simplifies the construction of pre-aliquoted kits based on such antibodies.

PMID: 7730665 [PubMed - indexed for MEDLINE]

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